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(54) Title: USE OF BASES FOR THE MANUFACTURE OF A MEDICAMENT IN THE TREATMENT OF DIFFERENT FORMS OF INFLAMMATORY DERMATOSIS

(57) Abstract: Provided are methods and topical pharmaceutical formulations for the treatment of inflammatory dermatoses. The invention involves the topical administration of a pharmacologically active base in a formulation having a pH of about 7.5 to about 13.0, preferably about 8.0 to 11.5, and most preferably about 8.5 to 10.5. These basic formulations are particularly suited to the treatment of acne vulgaris.

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USE OF BASES FOR THE MANUFACTURE OF A MEDICAMENT IN THE TREATMENT OF DIFFERENT FORMS OF INFLAMMATORY DERMATOSIS

TECHNICAL FIELD

[0001] This invention relates generally to methods and pharmaceutical formulations for treating inflammatory dermatoses, including autoimmune dermatoses, and, more particularly, relates to the use of a pharmacologically active base in such methods and formulations.

BACKGROUND

[0002] Acne vulgaris is a condition that affects nearly 100% of people between the ages of 12 and 17, although some adults continue to suffer from the condition well into their thirties or beyond. Acne lesions are commonly located on the face, but the lesions can also be found on the neck, chest, back, shoulders, scalp, upper arms, and legs. It has been estimated that Americans spend well over one hundred million dollars for the treatment of acne each year.

[0003] Acne occurs in response to clogged hair follicles. Initially, sebaceous glands associated with a hair follicle fill the follicle with sebum, an oil-like substance. Dead skin cells lining the hair follicle slough off into the follicle. Normally, the sebum, dead skin cells, and other substances are routinely eliminated from the follicle. When the sebum and dead skin cells form a plug in the follicle, however, a comedone develops. An open comedone occurs when the opening of the follicular canal dilates and the plug protrudes from the canal and turns a characteristic dark color. Open comedones are also referred to as "blackheads" as a result of their characteristic dark color upon exposure to the outside surface of the skin. Closed comedones occur when the follicle is covered, e.g., with a layer of cells, such that the plug does not reach the external environment. Closed comedones are also referred to as "whiteheads" given their characteristic white color.

[0004] The production of sebum and dead skin cells lining the follicle increases dramatically during puberty in response to hormonal changes. It is this increased production of these products that causes adolescents to be the most likely individuals to suffer from acne.

[0005] Plugs that are not removed from open and closed comedones may swell further. Additional sebum and dead skin cells may accumulate in the clogged follicle. In addition, bacteria such as *Propionibacterium acnes* may multiply, secreting enzymes that hydrolyze sebum into free fatty acids. The enzymes and the free fatty acids trigger the inflammatory process. As a result, white blood cells such as neutrophils migrate to the follicle, causing an erythematous papule to develop. With continued sebum production and bacterial colonization, the follicle ruptures, causing its contents to spill into the dermis. Continuation of this severe inflammation can cause a cyst.

[0006] Based on its etiology, acne may be classified into one of three categories: comedonal, inflammatory, and nodulocystic. Comedonal acne consists predominately of open or closed comedones with little or no accompanying inflammation. Eythromatous papules and pustules characterize inflammatory acne, but comedones may also be present. Nodulocystic acne may consist of comedones and inflammatory lesions, as well as deeper nodules and cysts.

[0007] Pharmacotherapy is used to treat acne. Systemic therapy includes oral contraceptives, erythromycin, tetracyclines, doxycycline, minocycline, and isotretinoin. Systemic therapy, however, has many drawbacks. For example, resistance may be developed to antibiotics such as erythromycin, tetracycline, doxycycline, and minocycline. Nishijima et al. (2000) *J. Dermatol.* 27(5):318-323. Oral contraceptives are inappropriate for male patients as well as for certain populations of female patients, e.g., female patients with a history of breast carcinoma or thromboembolic disorders. Due to its teratogenic activity, isotretinoin therapy requires that female patients not become pregnant during treatment. Furthermore, systemic administration causes systemic side effects, as relatively high levels of the drug must circulate throughout the entire body.

[0008] Topical therapy addresses some of the concerns associated with systemic therapy and represents a useful approach to treating individuals suffering from acne. U.S. Patent No. 5,740,884 describes administering an anti-acne composition containing benzoyl peroxide. U.S. Patent No. 5,753,637 to Fried describes topical administration of a combination of benzoyl peroxide, salicylic acid, and a vasoconstrictor to treat an individual suffering from acne. U.S. Patent No. 5,958,984 to Devillez describes topically applying a composition containing hydrogen peroxide.

[0009] While topical administration of any one of these compositions may work for some individuals some of time, additional regimens for treating acne and other inflammatory dermatoses are desired. The present invention addresses these and other needs in the art by providing novel methods and formulations for treating inflammatory dermatoses, including sebaceous gland disorders such as acne vulgaris, as will be discussed in detail herein.

SUMMARY OF THE INVENTION

[0010] It is accordingly a primary object of the invention to address the above needs in the art by providing a novel method and formulation for the treatment of inflammatory dermatoses, including sebaceous gland disorders such as acne vulgaris.

[0011] It is another object of the invention to provide a method and formulation for the treatment of inflammatory dermatoses, involving a topically applied formulation containing a pharmacologically active base in an amount effective to provide the formulation with a pH in the range of about 7.5 to 13.0. The formulation may be a lotion, cream, solution, paste, ointment, or the like, or may be contained in a skin patch comprised of a laminated composite intended for long-term adhesion to the

body surface (typically throughout a delivery period in the range of about 8 to about 72 hours) in the region of the affected area.

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS AND NOMENCLATURE:

[0012] Before describing the present invention in detail, it is to be understood that this invention is not limited to specific pharmacologically active bases, carriers, formulation types, treatment regimens, and so forth, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0013] It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0014] The terms "pharmacologically active agent," "pharmacologically active base," and "active agent" are used interchangeably herein to refer to a basic compound or composition of matter that, when topically administered to a human patient, induces a desired pharmacologic and/or physiologic effect by local and/or systemic action, i.e., prevention or treatment of an inflammatory dermatosis. Also included are derivatives and analogs of those compounds or classes of compounds specifically mentioned that also induce the desired effect.

[0015] By "pharmaceutically acceptable," such as in the recitation of a "pharmaceutically acceptable carrier," or a "pharmaceutically acceptable derivative," is meant a compound that is not biologically or otherwise undesirable, i.e., the compound may be incorporated into a topical formulation of the invention and administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the formulation in which it is contained. A "pharmacologically active" compound refers to an active agent as defined above, or to an analog or derivative thereof having the same type of pharmacological activity as the parent compound.

[0016] The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. The present method of "treating" a patient, as the term is used herein, thus encompasses both prevention of an inflammatory dermatosis in a predisposed individual and treatment of an inflammatory dermatosis in a clinically symptomatic individual.

[0017] The term "base" is used in its traditional sense, *i.e.*, a substance that dissolves in water to produce hydroxide ions. The water is typically an aqueous fluid, and may be natural moisture at the skin surface, or the patch or composition that is used may contain added water, and/or be used in

connection with an occlusive backing. Similarly, any liquid or semisolid formulation that is used is preferably aqueous or used in conjunction with an overlayer of an occlusive material. Any base may be used provided that the compound provides free hydroxide ions in the presence of an aqueous fluid. Bases can provide free hydroxide ions either directly or indirectly and thus can also be referred to as "hydroxide-releasing agents". Hydroxide-releasing agents that provide free hydroxide ions directly, typically contain hydroxide groups and release the hydroxide ions directly into solution, for example, alkali metal hydroxides. Hydroxide-releasing agents that provide free hydroxide ions indirectly, are typically those compounds that are acted upon chemically in an aqueous environment and the reaction produces hydroxide ions, for example metal carbonates or amines.

[0018] By an "effective" amount or a "therapeutically effective amount" of a pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, i.e., prevention or treatment of an inflammatory dermatosis. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, mode of administration, and the like. Thus, it is not always possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

[0019] The term "topical administration" is used in its conventional sense to mean delivery of a topical drug or pharmacologically active agent to the skin or mucosal tissue, as in, for example, the treatment of an inflammatory dermatosis such as acne vulgaris.

[0020] The term "body surface" is used to refer to skin or mucosal tissue.

[0021] "Carriers" or "vehicles" as used herein refer to pharmaceutically acceptable carrier materials suitable for topical drug administration. Carriers and vehicles useful herein include any such materials known in the art that are nontoxic and do not interact with other components of the composition in a deleterious manner.

[0022] The term "aqueous" refers to a formulation that contains water or that becomes water-containing following application to the skin or mucosal tissue.

[0023] In describing molecular structures and formulae herein, the phrase "having the formula" or "having the structure" is not intended to be limiting and is used in the same way that the term "comprising" is commonly used.

[0024] The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon group typically although not necessarily containing 1 to about 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, octyl, decyl, and the like, as well as cycloalkyl groups such as cyclopentyl, cyclohexyl, and the like. Generally, although again not necessarily, alkyl groups herein contain 1 to about 12 carbon atoms. The term "lower alkyl" intends an alkyl group of one to six carbon atoms, preferably one to four carbon atoms. "Substituted alkyl" refers to

alkyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkyl" and "heteroalkyl" refer to alkyl in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms "alkyl" and "lower alkyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkyl or lower alkyl.

[0025] The term "alkenyl" as used herein refers to a branched or unbranched hydrocarbon group typically although not necessarily containing 2 to about 24 carbon atoms and at least one double bond, such as ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, isobutenyl, octenyl, decenyl, and the like. Generally, although again not necessarily, alkenyl groups herein contain 2 to about 12 carbon atoms. The term "lower alkenyl" intends an alkenyl group of two to six carbon atoms, preferably two to four carbon atoms. "Substituted alkenyl" refers to alkenyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkenyl" and "heteroalkenyl" refer to alkenyl in which at least one carbon atom is replaced with a heteroatom.

[0026] The term "aryl" as used herein, and unless otherwise specified, refers to an aromatic substituent containing a single aromatic ring or multiple aromatic rings that are fused together, linked covalently, or linked to a common group such as a methylene or ethylene moiety. The common linking group may also be a carbonyl as in benzophenone, an oxygen atom as in diphenylether, or a nitrogen atom as in diphenylamine. Preferred aryl groups contain one aromatic ring and are referred to as "monocyclic aryl." "Substituted aryl" refers to an aryl moiety substituted with one or more substituent groups, and the terms "heteroatom-containing aryl" and "heteroaryl" refer to aryl in which at least one carbon atom is replaced with a heteroatom.

[0027] The term "heteroatom-containing" as in a "heteroatom-containing hydrocarbyl group" refers to a molecule or molecular fragment in which one or more carbon atoms is replaced with an atom other than carbon, e.g., nitrogen, oxygen, sulfur, phosphorus, or silicon. Similarly, the term "heteroalkyl" refers to an alkyl substituent that is heteroatom-containing, the term "heterocyclic" refers to a cyclic substituent that is heteroatom-containing, the term "heteroaryl" refers to an aryl substituent that is heteroatom-containing, and the like. When the term "heteroatom-containing" appears prior to a list of possible heteroatom-containing groups, it is intended that the term apply to every member of that group. That is, the phrase "heteroatom-containing alkyl, alkenyl, and alkynyl" is to be interpreted as "heteroatom-containing alkyl, heteroatom-containing alkenyl, and heteroatom-containing alkynyl."

[0028] By "substituted" as in "substituted alkyl," "substituted alkenyl," "substituted aryl," and the like, as alluded to in some of the aforementioned definitions, is meant that in the alkyl, alkenyl, aryl, or other moiety, at least one hydrogen atom bound to a carbon atom is replaced with one or more substituents that are functional groups such as hydroxyl, alkoxy, thio, amino, halo, and the like.

[0029] The terms "alkyl," "alkenyl," "aryl," and the like are, unless otherwise indicated, intended to include unsubstituted, substituted, heteroatom-containing, and substituted heteroatom-containing variants.

II. INDICATIONS:

[0030] The invention pertains to treatment of an individual predisposed to or afflicted with an inflammatory dermatosis, comprising topically administering a pharmaceutical formulation containing a pharmacologically active base to the affected skin area, wherein the formulation preferably has a pH in the range of about 7.5 to about 13.0, preferably about 8.0 to 11.5, more preferably about 8.5 to 11.5, and most preferably about 8.5 to 10.5. In some aspects, the pH will be in the range of about 9.5 to 11.5, preferably 10.0 to about 11.5. The term "inflammatory dermatosis" includes a range of skin disorders, including, but not limited to, sebaceous gland disorders, papulosquamous dermatoses, allergic dermatoses, pruritic dermatoses, vascular dermatoses, bacterial dermatoses, viral dermatoses, mycolic skin infections, granulomatous dermatoses, parasitic skin dermatoses, exfoliative dermatitis, bullous dermatoses, pigmented dermatoses, photosensitive dermatoses, dermatoses caused by collagen diseases, and dermatoses due to internal diseases. The inflammatory dermatosis can also be associated with an autoimmune condition, in which case it is referred to herein as "autoimmune dermatosis."

[0031] In a preferred embodiment, the inflammatory dermatosis that the method and formulation of the invention are used to treat is a sebaceous gland disorder, e.g., an acneiform disorder such as acne vulgaris, acne conglombata, hidradenitis suppurativa, acne rosacea, seborrhea, seborrheic dermatitis, gram negative folliculitis, pyoderma faciale, steatocystoma multiplex, sebaceous hyperplasia, or rhinophyma. In a particularly preferred embodiment, the invention is used to treat acne vulgaris. As is well known, acne vulgaris is a chronic skin condition characterized by comedones and papules, and can be quite severe; in particularly severe cases, pustules, cysts, and permanent scarring may occur.

[0032] In another preferred embodiment, the inflammatory dermatosis treated is a papulosquamous dermatosis such as, for example, psoriasis, Pityriasis rosea, tinea versicolor, or lichen planus. The method and formulations of the invention are particularly useful in treating psoriasis, an autoimmune inflammatory disorder that has proven difficult to treat with conventional agents.

[0033] In a further preferred embodiment, the inflammatory dermatosis treated is an autoimmune dermatosis that may be, by way of example, atopic dermatitis, mast cell disease, bullous pemphigoid, pemphigus vulgaris, necrotizing vasculitis, discoid lupus erythematosus, systemic lupus erythematosis, or dermatitis herpetiformis.

[0034] In other embodiments, examples of the various types of inflammatory dermatoses with which the method and formulation of the invention are effective are as follows:

[0035] Allergic Dermatoses: contact dermatitis; photoallergic dermatitis; industrial dermatoses caused by exposure to a variety of compounds used by industry that are contact irritants; atopic eczema (infantile and adult); and dermatoses caused by drugs and nummular eczema.

[0036] Pruritic Dermatoses: winter, senile, and essential pruritus; pruritus ani; eternal otitis; pruritis hiemalis; pruritis vulvae; and pruritus scrotae.

[0037] Vascular Dermatoses: erythema multiforme; erythema nodosum; stasis dermatitis; purpuric dermatoses such as those associated with thrombocytopenic purpura, nonthrombocytopenic purpura, dysproteinemic purpura, actinic purpura, scorbutic purpura, and Henochs purpura; ecchymoses; stasis purpura; primary and secondary telangiectases.

[0038] Bacterial Dermatoses: pyoderma such as impetigo, ecthyma, folliculitis, furuncles styes, carbuncles, sweat gland infections, erysipelas, erythrasma, infected ulcers, and infected eczematoid dermatitis; and bacterial dermatoses associated with systemic bacterial infections such as scarlet fever, granuloma inguinale, chancroid, tuberculosis, leprosy, gonorrhea, rickettsial diseases, actinomycosis, and syphilis.

[0039] Viral Dermatoses: such as those caused by Herpes simplex virus, Kaposi's varicelliform eruption, zoster, chickenpox, smallpox, vaccinia, molluscum contagiosum, lymphogranuloma venereum, exanthematous diseases such as German measles, roseola, and erythema infectiosum.

[0040] Mycolic Skin Infections: tinea cruris (superficial fungal infections of the skin in various body sites); athlete's foot (dermatophytosis of the feet caused to infection with *trichophyton mentagrophytes*); tinea unguium (onychomycosis); sporotrichosis; coccidioidomycosis; histoplasmosis; and North American blastomycosis.

[0041] Granulomatous Dermatoses: sarcoidosis; granuloma annulare; reticulohistiocytoma; and silica-induced granulomas.

[0042] Parasitic Skin Infections: scabies, *cheyletiella* dermatitis; demodicosis; pediculosis

[0043] Pigmented Dermatoses: Chloasma (melasma) and vitiligo.

[0044] Collagen Diseases: scleroderma and dermatomyositis.

[0045] Dermatoses Due to Internal Diseases: pyoderma gangrenosum associated with ulcerative colitis, and ulcers due to diabetes.

[0046] Photosensitive Dermatoses: Exogenous types such as drug-induced photodermatitis and contact dermatitis with photoallergic components; and endogenous types such as those associated with porphyrias and polymorphous light eruptions.

III. THE PHARMACOLOGICALLY ACTIVE BASE:

[0047] The pharmacologically active base of the invention is an inorganic or an organic pharmaceutically acceptable base. Preferred inorganic bases include inorganic hydroxides,

inorganic oxides, inorganic salts of weak acids, and combinations thereof. Preferred organic bases are nitrogenous bases.

[0048] It has long been thought that strong bases, such as NaOH, were not suitable as pharmacologically active bases because they would damage skin. It has been now been discovered that the skin permeability of various drugs could be enhanced without skin damage by exposing the skin to a base or basic solution, in a skin contacting formulation or patch. The desired pH of the solution on the skin can be obtained using a variety of bases or base concentrations. Accordingly, the pH is selected so as to be low enough so as to not cause skin damage, but high enough to enhance skin permeation to various active agents. As such, it is important that the amount of base in any patch or formulation is optimized so as to increase the flux of the drug through the body surface while minimizing any possibility of skin damage. In general, this means that the pH at the body surface in contact with a formulation or drug delivery system of the invention is preferably in the range of approximately 8.0 to 13.0, preferably about 8.0 to 11.5, more preferably about 8.5 to 11.5 and most preferably about 8.5 to 10.5. In some aspects, the pH will be in the range of about 9.5 to 11.5, preferably 10.0 to about 11.5.

[0049] In one preferred embodiment, the pH at the body surface is the primary design consideration, i.e., the composition or system is designed so as to provide the desired pH at the body surface. Anhydrous formulations and transdermal systems may not have a measurable pH, and the formulation or system can be designed so as to provide a target pH at the body surface. Moisture from the body surface can migrate into the formulation or system, dissolve the base and thus release the base into solution, which will then provide the desired target pH at the skin's surface. In those instances, a hydrophilic composition is preferred. In addition, when using aqueous formulations, the pH of the formulation may change over time after it is applied on the skin. For example, gels, solutions, ointments, etc., may experience a net loss of moisture after being applied to the body surface, i.e., the amount of water lost is greater than the amount of water received from the body surface. In that case, the pH of the formulation may be different than its pH when manufactured. This problem can be easily remedied by designing the aqueous formulations to provide a target pH at the skin's surface.

[0050] In other embodiments of the invention, the pH of the formulation or the drug composition contained within a delivery system will be in the range of approximately 8.0 to 13.0, preferably about 8.0 to 11.5, more preferably about 8.5 to 11.5, and most preferably about 8.5 to 10.5. In some aspects, the pH will be in the range of about 9.5 to 11.5, preferably 10.0 to 11.5. In one embodiment of the invention the pH of the formulation is higher than the pH at the body surface. For example, if an aqueous formulation is used, moisture from the body surface can dilute the formulation, and thus provide for a different pH at the body surface, which will typically be lower than that of the formulation itself.

[0051] In one preferred embodiment, the body surface is exposed to a base or basic solution for a sufficient period of time so as to provide a high pH at the body surface, thus creating channels in the skin or mucosa for the drug to go through. It is expected that drug flux is proportional to the strength of the solution and the duration of exposure. However, it is desirable to balance the maximization of drug flux with the minimization of skin damage. This can be done in numerous ways. For example, the skin damage may be minimized by selecting a lower pH within the 8.0 to 13.0 range, by exposing the skin to the formulation or system for a shorter period of time, or by including at least one irritation-mitigating additive. Alternatively, the patient can be advised to change the location of application with each subsequent administration.

[0052] While certain preferred amounts are set forth below, it is understood that, for all of the inorganic and organic bases described herein, the optimum amount of any such base will depend on the strength or weakness of the base and its molecular weight, and other factors such as the number of ionizable sites in the active agent being administered and whether there are any acidic species present in the formulation or patch. One skilled in the art may readily determine the optimum amount for any particular base such that the degree of enhancement is optimized while the possibility of damage to the body surface is eliminated or at least substantially minimized.

Inorganic Base

[0053] Exemplary inorganic bases are inorganic hydroxides, inorganic oxides, inorganic salts of weak acids, and combinations thereof. Preferred inorganic bases are those whose aqueous solutions have a high pH, and are acceptable as food or pharmaceutical additives. Examples of such preferred inorganic bases are those listed below, along with their respective pHs. Some of the bases are identified by their hydrate forms, and it is understood that when referring to a "base", both the hydrated and non-hydrated forms are intended to be included.

Inorganic base	pH of Aqueous Solution (concentration)
Ammonium hydroxide[1, 2, 3]	11.27 (1 N), 10.27 (0.001 N)
Sodium hydroxide[1, 2, 3]	14 (5%), 13 (0.5%), 12 (0.05%)
Potassium hydroxide[1, 2, 3]	13.5 (0.1 M)
Calcium hydroxide[1, 3]	12.4 (saturated solution in water)
Magnesium hydroxide[1, 3]	9.5 to 10.5 slurry
Magnesium oxide[1, 2, 3]	10.3 (saturated aqueous solution)
Calcium oxide[3]	Soluble in water, Form $Ca(OH)_2$
Sodium acetate[1, 3]	~ 8.9 (0.1 N)
Sodium acetate, trihydrate[1, 2]	8.9 (0.1 N)
Sodium acetate, anhydrous[1, 2]	~ 8.9 (0.1 N)

Inorganic base	pH of Aqueous Solution (concentration)
Sodium borate decahydrate[1, 2]	~ 8.8-9.4, 9.15 to 9.2 (0.01M)
Sodium borate[1, 2, 3]	8.8-9.4, 9.15 to 9.2 (0.01M)
Sodium metaborate	Strongly alkaline
Sodium carbonate[1, 2, 3]	~ 11.6
Sodium carbonate hydrate[1]	~ 11.6
Sodium carbonate anhydrous	~ 11.6
Sodium bicarbonate[1, 2, 3]	8.3 (0.1 M fresh)
Sodium phosphate, tribasic[1, 3]	~ 11.5 (0.1%), ~ 11.7 (0.5%), ~ 11.9 (1.0%)
Sodium phosphate, tribasic dodecahydrate	11.5 (0.1%), 11.7 (0.5%), 11.9 (1.0%)
Sodium phosphate, dibasic, anhydrous[1, 2]	9.1 (1%)
Sodium phosphate, dibasic, heptahydrate[1, 2]	~ 9.5
Sodium phosphate, dibasic[1, 3]	~ 9.5
Sodium phosphate, dibasic, dihydrate[1]	~ 9.5
Sodium phosphate, dibasic, dodecahydrate	~ 9.5
Potassium carbonate[1, 3]	~ 11.6
Potassium bicarbonate[3]	8.2 (0.1 M)
Potassium citrate[1, 2, 3]	~ 8.5
Potassium citrate monohydrate	~ 8.5
Potassium acetate[1, 3]	9.7 (0.1 M)
Potassium phosphate, dibasic[1, 2]	Aqueous solution is slightly alkaline
Potassium phosphate, tribasic[3]	Aqueous solution is strongly alkaline
Ammonium phosphate, dibasic[1, 2, 3]	~ 8

[1]listed in the "Chemicals in Compliance with Pharmaceutical Standards: Inactive Ingredient Guide"
[2]listed in the "Handbook of Pharmaceutical Additives"
[3]listed in the FDA's food additive database

Inorganic Hydroxides

[0054] Inorganic hydroxides include, for example, ammonium hydroxide, alkali metal hydroxide and alkaline earth metal hydroxides, and mixtures thereof. Preferred inorganic hydroxides include ammonium hydroxide; monovalent alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; divalent alkali earth metal hydroxides such as calcium hydroxide and magnesium hydroxide; and combinations thereof.

[0055] The amount of inorganic hydroxide included in the compositions and systems of the invention, will typically represent about 0.3-7.0 wt%, preferably 0.5-4.0 wt%, more preferably about

0.5-3.0 wt%, most preferably about 0.75-2.0 wt%, of a topically applied formulation or of a drug reservoir of a drug delivery system, or patch.

[0056] The aforementioned amounts are particularly applicable to those formulations and patches in which the active agent is (1) an uncharged molecule, e.g., wherein a basic drug is in nonionized, free-base form, (2) a basic salt of an acidic drug, or (3) there are no additional species in the formulation or patch that could react with or be neutralized by the inorganic hydroxide, to any significant degree.

[0057] For formulations and patches in which the drug is in the form of an acid addition salt, and/or wherein there are additional species in the formulations or systems that can be neutralized by or react with the inorganic base (i.e., acidic inactive ingredients), the amount of inorganic hydroxide is preferably the total of (1) the amount necessary to neutralize the acid addition salt and/or other base-neutralizable species (i.e., the "acidic species"), plus (2) about 0.3-7.0 wt%, preferably 0.5-4.0 wt%, more preferably about 0.5-3.0 wt%, most preferably about 0.75-2.0 wt%, of the formulation or drug reservoir. That is, for an acid addition salt, the enhancer is preferably present in an amount just sufficient to neutralize the salt, plus an additional amount (i.e., about 0.3-7.0 wt%, preferably 0.5-4.0 wt%, more preferably about 0.5-3.0 wt%, most preferably about 0.75-2.0 wt%) to enhance the flux of the drug through the skin or mucosal tissue. Basic drugs in the form of a neutral, free base or basic salt of acidic drug are usually not affected by a base, and thus for these drugs, the amount in (1) is usually the amount necessary to neutralize inactive components that are acidic. For patches, the aforementioned percentages are given relative to the total weight of the formulation components and the adhesive, gel or liquid reservoir.

[0058] Still greater amounts of inorganic hydroxide may be used by controlling the rate and/or quantity of release of the base, preferably during the drug delivery period itself.

Inorganic Oxides

[0059] Inorganic oxides include, for example, magnesium oxide, calcium oxide, and the like.

[0060] The amount of inorganic oxide included in the compositions and systems of the invention may be substantially higher than the numbers set forth above for the inorganic hydroxide, and may be as high as 20 wt%, in some cases as high as 25 wt% or higher, but will generally be in the range of about 2-20 wt%. These amounts may be adjusted to take into consideration the presence of any base-neutralizable species.

Inorganic Salts of Weak Acids

[0061] Inorganic salts of weak acids include, ammonium phosphate (dibasic); alkali metal salts of weak acids such as sodium acetate, sodium borate, sodium metaborate, sodium carbonate, sodium bicarbonate, sodium phosphate (tribasic), sodium phosphate (dibasic), potassium carbonate,

potassium bicarbonate, potassium citrate, potassium acetate, potassium phosphate (dibasic), potassium phosphate (tribasic); alkaline earth metal salts of weak acids such as magnesium phosphate and calcium phosphate; and the like, and combinations thereof.

[0062] Preferred inorganic salts of weak acids include, ammonium phosphate (dibasic) and alkali metal salts of weak acids.

[0063] The amount of inorganic salts of weak acids included in the compositions and systems of the invention may be substantially higher than the numbers set forth above for the inorganic hydroxide, and may be as high as 20 wt%, in some cases as high as 25 wt% or higher, but will generally be in the range of approximately 2-20 wt%. These amounts may be adjusted to take into consideration the presence of any base-neutralizable species.

Organic Bases

[0064] Organic bases suitable for use in the invention are compounds having an amino group, amido group, an oxime, a cyano group, an aromatic or non-aromatic nitrogen-containing heterocycle, a urea group, and combinations thereof. More specifically, examples of suitable organic bases are nitrogenous bases, which include, but are not limited to, primary amines, secondary amines, tertiary amines, amides, oximes, cyano (-CN) containing groups, aromatic and non-aromatic nitrogen-containing heterocycles, urea, and mixtures thereof. Preferred organic bases are primary amines, secondary amines, tertiary amines, aromatic and non-aromatic nitrogen-containing heterocycles, and mixtures thereof.

[0065] For nitrogenous bases, the amount of the agent will typically represent about 0.5-4.0 wt%, preferably about 0.5-3.0 wt%, more preferably about 0.75-2.0 wt%, of a topically applied formulation or of a drug reservoir of a drug delivery system or a patch. These amounts may be adjusted to take into consideration the presence of any base-neutralizable species.

[0066] Still greater amounts of the nitrogenous base may be used depending on the strength of the base and the rate and/or quantity of release of the nitrogenous base preferably during the drug delivery period itself.

[0067] Preferred organic bases are those whose aqueous solutions have a high pH or a high pKa (more preferably a pKa>9), and are acceptable as food or pharmaceutical additives. Examples of such preferred organic bases are those listed below, along with their respective pHs (or pKa values).

Organic base	pH of Aqueous Solution (concentration)
2-amino-2-methyl-1,3-propanediol[1]	10.8 (0.1 m)
2-amino-2-methyl-1-propanol[1]	11.3 (0.1 m)
Diethanolamine[1]	11.0 (0.1 N)
Triethanolamine[1]	10.5 (0.1 N)

Organic base	pH of Aqueous Solution (concentration)
Butylamine[2]	pKa = 10.56
Dimethylamine[2]	Strong base, pKa = 10.73
Cyclohexylamine[2]	Strong base, pKa = 10.64
Ethylenediamine[2]	Strong base, pKa = 10.71
Isopentylamine[2]	pKa = 10.6
Monoethanolamine[2]	12.1 (25%), 12.05 (0.1 N), pKa = 9.4
Phenethylamine[2]	Strong base, pKa = 9.83
Piperidine[2]	Strong base, pKa = 11.12
Pyrrolidine[2]	Strong base, pKa = 11.27
Trimethylamine[2]	Strong base, pKa = 9.81

[1]listed in the "Handbook of Pharmaceutical Additives"
[2]listed in the FDA's food additive database

Amines

[0068] Suitable nitrogenous bases may contain any one or a combination of the following:

[0069] primary amino ($-NH_2$) groups;

[0070] mono-substituted (secondary) amino groups -NHR where R is hydrocarbyl, generally either alkyl or aryl, e.g., lower alkyl or phenyl, and may be substituted with one or more nonhydrocarbyl substituents, e.g., 1 to 3 halo, hydroxyl, thiol, or lower alkoxy groups (such -NHR groups include, for example, methylamino, ethylamino, isopropylamino, butylamino, cyclopropylamino, cyclohexylamino, n-hexylamino, phenylamino, benzylamino, chloroethylamino, hydroxyethylamino, etc.);

[0071] di-substituted (tertiary) amino groups $-NR^aR^b$ where R^a and R^b may be the same or different and are as defined above for R (suitable $-NR^aR^b$ include, for example, dimethylamino, diethylamino, diisopropylamino, dibutylamino, methylpropylamino, methylhexylamino, methylcyclohexylamino, ethylcyclopropylamino, ethylchloroethylamino, methylbenzylamino, methylphenylamino, methyltoluylamino, methyl-*p*-chlorophenylamino, methylcyclohexylamino, etc.);

[0072] amides $-(CO)-NR^cR^d$ where R^c and R^d may be the same or different and are either hydrogen or R, wherein R is as defined above (including, for example, amides wherein one of R^c and R^d is H and the other is methyl, butyl, benzyl, etc.);

[0073] cyano (-CN);

[0074] aromatic nitrogen-containing heterocycles, typically five- or six-membered monocyclic substituents, or bicyclic fused or linked five- or six-membered rings (such as pyrrolyl, pyrrolidinyl, pyridinyl, quinolinyl, indolyl, pyrimidinyl, imidazolyl, 1,2,4-triazolyl, tetrazolyl, etc.); and

[0075] non-aromatic nitrogen-containing heterocycles, typically four- to six-membered rings, including lactams and imides, e.g., pyrrolidino, morpholino, piperazino, piperidino, N-phenyl-β-propiolactam, γ-butyrolactam, ε-caprolactam, acetimide, phthalimide, succinimide, etc.

[0076] Primary amines, secondary amines, and tertiary amines may be generically grouped as encompassed by the molecular structure $NR^1R^2R^3$ wherein R^1, R^2 and R^3 are selected from H, alkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, hydroxyalkenyl, alkoxyalkenyl, cycloalkyl, cycloalkyl-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl, with the proviso that at least one of R^1, R^2 and R^3 is other than H. Examples of such amines include, without limitation, diethanolamine, triethanolamine, isopropanolamine, triisopropanolamine, dibutanol amine, tributanol amine, N-dodecylethanolamine, N-(2-methoxyethyl) dodecylamine, N-(2,2-dimethoxyethyl)dodecylamine, N-ethyl-N-(dodecyl)ethanolamine, N-ethyl-N-(2-methoxyethyl)dodecylamine, N-ethyl-N-(2,2-dimethoxyethyl) dodecylamine, dimethyldodecylamine-N-oxide, monolauroyl lysine, dipalmitoyl lysine, dodecylamine, stearylamine, phenylethylamine, triethylamine, PEG-2 oleamine, PEG-5 oleamine, dodecyl 2-(N,N-dimethylamino)propionate, bis(2-hydroxyethyl)oleylamine, and combinations thereof.

[0077] Exemplary primary amines include 2- aminoethanol, 2-aminoheptane, 2-amino-2-methyl-1,3 propanediol, 2-amino-2-methyl-1-propanol, *n*-amylamine, benzylamine, 1,4-butanediamine, *n*-butylamine, cyclohexylamine, ethylamine, ethylenediamine, methylamine, α-methylbenzylamine, phenethylamine, propylamine, and tris(hydroxymethyl)aminomethane.

[0078] Exemplary secondary amines include compounds that contain groups such as methylamino, ethylamino, isopropylamino, butylamino, cyclopropylamino, cyclohexylamino, *n*-hexylamino, phenylamino, benzylamino, chloroethylamino, hydroxyethylamino, and so forth. Exemplary secondary amines include diethanolamine, diethylamine, diisopropylamine, and dimethylamine.

[0079] Exemplary tertiary amines include compounds that contain groups such as dibutylamino, diethylamino, dimethylamino, diisopropylamino, ethylchloroethylamino, ethylcyclopropylamino, methylhexylamino, methylcyclohexylamino, methylpropylamino, methylbenzylamino, methyl-*p*-chlorophenylamino, methylcyclohexylamino, methylphenylamino, methyltoluylamino, and so forth. Exemplary tertiary amines include N,N-diethylaniline, N,N-dimethylglycine, triethanolamine, triethylamine, and trimethylamine.

Amides

[0080] Amides, as will be appreciated by those skilled in the art, have the molecular structure R^4-(CO)-NR^5R^6 where R^4, R^5 and R^6 are generally selected from H, alkyl, cycloalkyl, cycloalkyl-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl. Examples of suitable amides herein include, without limitation, hexamethyleneacetamide, hexamethyleneoctamide, hexamethylene lauramide, hexamethylene palmitamide, N,N-dimethyl formamide, N,N-dimethyl

acetamide, N,N-dimethyloctamide, N,N-dimethyldecamide, toluamide, dimethyl-m-toluamide, diethyl-m-toluamide, and combinations thereof.

Nitrogen-Containing Heterocycles

[0081] Nitrogen-containing heterocycles suitable as the pharmacologically active base herein include, by way of example, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 1-propyl-3-dodecylpyrrolidine, 1-dodecyclazacycloheptan-2-one, ethylene thiourea, hydantoin, oxalylurea, imidazolidilyl urea, N-octadecyl morpholine, dodecylpyridinium, N-dodecylpyrrolidine, N-dodecylpiperidine, N-dodecylhomopiperidine, and combinations thereof.

[0082] Aromatic nitrogen-containing heterocycles typically contain a 5- or 6-membered monocyclic substituent, or a bicyclic fused or linked 5- or 6-membered ring, such as imidazolyl, indolyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, 1,2,4-triazolyl, etc.

[0083] Aromatic nitrogen-containing heterocycles suitable as the organic base herein include, by way of example, 2-amino-pyridine, benzimidazole, 2,5-diaminopyridine, 2,4-dimethylimidazole, 2,3-dimethylpyridine, 2,4-dimethylpyridine, 3,5-dimethylpyridine, imidazole, methoxypyridine, γ-picoline, 2,4,6-trimethylpyridine, and combinations thereof.

[0084] Non-aromatic nitrogen-containing heterocycles typically contain 4- to 6-membered rings such as acetimido, morpholinyl, lactams and imides (e.g., γ-butyrolactam, ε-caprolactam, N-phenyl-β-propiolactam), phthalimido, piperidyl, piperidino, piperazinyl, pyrrolidinyl, succinimido, etc.

[0085] Non-aromatic nitrogen-containing heterocycles include, by way of example, 1,2-dimethylpiperidine, 2,5-dimethylpiperazine, 1,2-dimethylpyrrolidine, 1-ethylpiperidine, *n*-methylpyrrolidine, morpholine, piperazine, piperidine, pyrrolidine, 2,2,6,6-tetramethylpiperidine, 2,2,4-trimethylpiperidine, and combinations thereof.

[0086] For all pharmacologically active bases herein, the optimum amount of any particular agent will depend on the strength or weakness of the base, the molecular weight of the base, and other factors such as the number of ionizable sites in the drug administered and any other acidic species in the formulation or patch. One skilled in the art may readily determine the optimum amount for any particular agent by ensuring that a formulation is effective to provide a pH at the skin surface, upon application of the formulation, in the range of about 7.5 to about 13.0, preferably about 8.0 to about 11.5, preferably in the range of about 8.5 to about 10.5. This in turn ensures that the degree of treatment is maximized while the possibility of damage to the body surface is eliminated or at least substantially minimized.

IV. PHARMACEUTICAL FORMULATIONS AND SKIN PATCHES:

[0087] The pharmaceutical formulation of the invention contains a pharmaceutically acceptable topical carrier and a pharmacologically active base, without any additional pharmacologically active agents. The pharmacologically active base is present at a concentration sufficient to provide a formulation pH in the range of approximately 7.5 to 13.0, preferably 8.0 to 11.5, most preferably 8.5 to 10.5. The formulation may be in any form suitable for application to the body surface, and may comprise, for example, a cream, lotion, solution, gel, ointment, paste, or the like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres. For those formulations in which the pharmacologically active base is a hydroxide-releasing agent, it is preferred although not essential that water be present. Thus, such a formulation may be aqueous, i.e., contain water, or may be nonaqueous and optionally used in combination with an occlusive overlayer so that moisture evaporating from the body surface is maintained within the formulation upon application to the body surface and thereafter.

[0088] Ointments, as is well known in the art of pharmaceutical formulation, are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery, and, preferably, will provide for other desired characteristics as well, e.g., emolliency or the like. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing. As explained in *Remington: The Science and Practice of Pharmacy*, 19th Ed. (Easton, PA: Mack Publishing Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin, and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see *Remington: The Science and Practice of Pharmacy* for further information.

[0089] Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase, also called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic, or amphoteric surfactant.

[0090] As will be appreciated by those working in the field of pharmaceutical formulation, gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the carrier liquid, which is typically aqueous, but also, preferably, contains an alcohol and, optionally, an oil. Preferred "organic macromolecules," i.e., gelling agents, are crosslinked acrylic acid polymers such as the "carbomer" family of polymers, e.g., carboxypolyalkylenes that may be obtained commercially under the Carbopol® trademark. Also preferred are hydrophilic polymers such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methyl cellulose; gums such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, or stirring, or combinations thereof.

[0091] Lotions, which are preferred for delivery of cosmetic agents, are preparations to be applied to the skin surface without friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid composition. It is generally necessary that the insoluble matter in a lotion be finely divided. Lotions will typically contain suspending agents to produce better dispersions as well as compounds useful for localizing and holding the active agent in contact with the skin, e.g., methylcellulose, sodium carboxymethylcellulose, or the like.

[0092] Pastes are semisolid dosage forms in which the active agent is suspended in a suitable base. Depending on the nature of the base, pastes are divided between fatty pastes or those made from a single-phase aqueous gels. The base in a fatty paste is generally petrolatum, hydrophilic petrolatum, or the like. The pastes made from single-phase aqueous gels generally incorporate carboxymethylcellulose or the like as a base.

[0093] Formulations may also be prepared with liposomes, micelles, and microspheres. Liposomes are microscopic vesicles having a lipid wall comprising a lipid bilayer, and can be used as drug delivery systems herein as well. Generally, liposome formulations are preferred for poorly soluble or insoluble pharmaceutical agents. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged), and neutral preparations. Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethyl-ammonium (DOTMA) liposomes are available under the tradename Lipofectin® (GIBCO BRL, Grand Island, NY). Similarly, anionic and neutral liposomes are readily available as well, e.g., from Avanti Polar Lipids (Birmingham, AL), or can be easily prepared using readily available materials.

Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with DOTMA in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0094] Micelles are known in the art as comprised of surfactant molecules arranged so that their polar head groups form an outer spherical shell, while their hydrophobic, hydrocarbon chains are oriented towards the center of the sphere, forming a core. Micelles form in an aqueous solution containing surfactant at a high enough concentration so that micelles naturally result. Surfactants useful for forming micelles include, but are not limited to, potassium laurate, sodium octane sulfonate, sodium decane sulfonate, sodium dodecane sulfonate, sodium lauryl sulfate, docusate sodium, decyltrimethylammonium bromide, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, tetradecyltrimethylammonium chloride, dodecylammonium chloride, polyoxyl 8 dodecyl ether, polyoxyl 12 dodecyl ether, nonoxynol 10, and nonoxynol 30. Micelle formulations can be used in conjunction with the present invention either by incorporation into the reservoir of a topical or transdermal delivery system, or into a formulation to be applied to the body surface.

[0095] Microspheres, similarly, may be incorporated into the present formulations and drug delivery systems. Like liposomes and micelles, microspheres essentially encapsulate a drug or drug-containing formulation. Microspheres are generally, although not necessarily, formed from synthetic or naturally occurring biocompatible polymers, but may also be comprised of charged lipids such as phospholipids. Preparation of microspheres is well known in the art and described in the pertinent texts and literature.

[0096] Various additives, known to those skilled in the art, may be included in the topical formulations. For example, solvents, including relatively small amounts of alcohol, may be used to solubilize certain formulation components. Although the pharmacologically active bases herein do penetrate into the skin and have in fact been described as skin permeation enhancers, it may be desirable, with weaker bases or particularly severe dermatoses, to include an added permeation enhancer in the formulation. Examples of suitable enhancers include, but are not limited to, ethers such as diethylene glycol monoethyl ether (available commercially as Transcutol®) and diethylene glycol monomethyl ether; surfactants such as sodium laurate, sodium lauryl sulfate, cetyltrimethylammonium bromide, benzalkonium chloride, Poloxamer (231, 182, 184), Tween (20, 40, 60, 80), and lecithin (U.S. Patent No. 4,783,450); alcohols such as ethanol, propanol, octanol, benzyl alcohol, and the like; polyethylene glycol and esters thereof such as polyethylene glycol monolaurate (PEGML; see, e.g., U.S. Patent No. 4,568,343); amides and other nitrogenous compounds such as urea, dimethylacetamide (DMA), dimethylformamide (DMF), 2-pyrrolidone,

1-methyl-2-pyrrolidone, ethanolamine, diethanolamine, and triethanolamine; terpenes; alkanones; and organic acids, particularly citric acid and succinic acid. Azone® and sulfoxides such as DMSO andC_{10}MSO may also be used, but are less preferred.

[0097] Most preferred enhancers are those lipophilic co-enhancers typically referred to as "plasticizing" enhancers, i.e., enhancers that have a molecular weight in the range of about 150 to 1000, and an aqueous solubility of less than about 1 wt.%, preferably less than about 0.5 wt.%, and most preferably less than about 0.2 wt.%. The Hildebrand solubility parameter σ of plasticizing enhancers is in the range of about 2.5 to about 10, preferably in the range of about 5 to about 10. Such enhancers are described in detail in co-pending, commonly assigned U.S. Patent Publication No. US 2001/0051166 A1, and in International Patent Application No. PCT/US00/34483, published June 21, 2001 as WO 01/43775 A2. Preferred lipophilic enhancers are fatty esters, fatty alcohols, and fatty ethers. Examples of specific and most preferred fatty acid esters include methyl laurate, ethyl oleate, propylene glycol monolaurate, propylene glycerol dilaurate, glycerol monolaurate, glycerol monooleate, isopropyl *n*-decanoate, and octyldodecyl myristate. Fatty alcohols include, for example, stearyl alcohol and oleyl alcohol, while fatty ethers include compounds wherein a diol or triol, preferably a C_2-C_4 alkane diol or triol, is substituted with one or two fatty ether substituents.

[0098] Additional permeation enhancers will be known to those of ordinary skill in the art of topical drug delivery, and/or are described in the pertinent texts and literature. See, e.g., *Percutaneous Penetration Enhancers*, eds. Smith et al. (CRC Press, 1995).

[0099] The present formulations may also include conventional additives such as opacifiers, antioxidants, fragrance, colorant, gelling agents, thickening agents, stabilizers, surfactants, and the like. Other agents may also be added, such as antimicrobial agents, to prevent spoilage upon storage, i.e., to inhibit growth of microbes such as yeasts and molds. Suitable antimicrobial agents are typically selected from the group consisting of the methyl and propyl esters of p-hydroxybenzoic acid (i.e., methyl and propyl paraben), sodium benzoate, sorbic acid, imidurea, and combinations thereof.

[0100] The formulations may also contain irritation-mitigating additives to minimize or eliminate the possibility of skin irritation or skin damage resulting from the pharmacologically active base or other components of the composition. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin; and chloroquine. The irritant-mitigating additive, if present, may be incorporated into the present formulations at a concentration effective to mitigate irritation or skin damage, typically representing not more than about 20 wt.%, more typically not more than about 5 wt.%, of the composition.

[0101] The pharmacologically active base may also be administered through the skin or mucosal tissue using a conventional skin patch, wherein the agent is contained within a laminated structure that serves as a drug delivery device to be affixed to the body surface. In such a structure, the pharmaceutical formulation is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs.

[0102] In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable adhesive material that serves to affix the system to the skin during drug delivery; typically, the adhesive material is a pressure-sensitive adhesive (PSA) that is suitable for long-term skin contact, and that should be physically and chemically compatible with the pharmacologically active base and any carriers, vehicles, or other additives that are present. Examples of suitable adhesive materials include, but are not limited to, the following: polyethylenes; polysiloxanes; polyisobutylenes; polyacrylates; polyacrylamides; polyurethanes; plasticized ethylene-vinyl acetate copolymers; and tacky rubbers such as polyisobutene, polybutadiene, polystyrene-isoprene copolymers, polystyrene-butadiene copolymers, and neoprene (polychloroprene). Preferred adhesives are polyisobutylenes.

[0103] The backing layer functions as the primary structural element of the transdermal system and provides the device with flexibility and, preferably, occlusivity. The material used for the backing layer should be inert and incapable of absorbing drug, base, or other components of the formulation contained within the device. The backing is preferably comprised of a flexible elastomeric material that serves as a protective covering to prevent loss of drug and/or vehicle via transmission through the upper surface of the patch, and preferably imparts a degree of occlusivity to the system, such that the area of the body surface covered by the patch becomes hydrated during use. The material used for the backing layer should permit the device to follow the contours of the skin and be worn comfortably on areas of skin such as at joints or other points of flexure that are normally subjected to mechanical strain, with little or no likelihood of the device disengaging from the skin due to differences in the flexibility or resiliency of the skin and the device. The materials used as the backing layer are either occlusive or permeable, as noted above, although occlusive backings are preferred, and are generally derived from synthetic polymers (e.g., polyester, polyethylene, polypropylene, polyurethane, polyvinylidine chloride, and polyether amide), natural polymers (e.g., cellulosic materials), or macroporous woven and nonwoven materials.

[0104] During storage and prior to use, the laminated structure includes a release liner. Immediately prior to use, this layer is removed from the device so that the system may be affixed to the skin. The release liner should be made from a drug/vehicle impermeable material, and is a disposable element that serves only to protect the device prior to application. Typically, the release liner is formed from a material impermeable to the pharmacologically active agent and the base, and that is easily stripped from the patch prior to use.

[0105] In an alternative embodiment, the active agent-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir. In such a case, the reservoir may be a polymeric matrix as described above. Alternatively, the reservoir may be comprised of a liquid or semisolid formulation contained in a closed compartment or "pouch," or it may be a hydrogel reservoir, or it may take some other form. Hydrogel reservoirs are particularly preferred herein. As will be appreciated by those skilled in the art, hydrogels are macromolecular networks that absorb water and thus swell but do not dissolve in water. That is, hydrogels contain hydrophilic functional groups that provide for water absorption, but the hydrogels are comprised of crosslinked polymers that give rise to aqueous insolubility. Generally, then, hydrogels are comprised of crosslinked hydrophilic polymers such as a polyurethane, a polyvinyl alcohol, a polyacrylic acid, a polyoxyethylene, a polyvinylpyrrolidone, a poly(hydroxyethyl methacrylate) (poly(HEMA)), or a copolymer or mixture thereof. Particularly preferred hydrophilic polymers are copolymers of HEMA and polyvinylpyrrolidone.

[0106] Additional layers, e.g., intermediate fabric layers and/or rate-controlling membranes, may also be present in any of these drug delivery systems. Fabric layers may be used to facilitate fabrication of the device, while a rate-controlling membrane may be used to control the rate at which a component permeates out of the device. The component may be an active agent, an enhancer, or some other component contained in the drug delivery system. A rate-controlling membrane, if present, will be included in the system on the skin side of one or more of the drug reservoirs. The materials used to form such a membrane are selected to limit the flux of one or more components contained in the drug formulation. Representative materials useful for forming rate-controlling membranes include polyolefins such as polyethylene and polypropylene, polyamides, polyesters, ethylene-ethacrylate copolymer, ethylene-vinyl acetate copolymer, ethylene-vinyl methylacetate copolymer, ethylene-vinyl ethylacetate copolymer, ethylene-vinyl propylacetate copolymer, polyisoprene, polyacrylonitrile, ethylene-propylene copolymer, and the like.

[0107] Generally, the underlying surface of the transdermal device, i.e., the skin contact area, has an area in the range of about 5 cm^2 to 200 cm^2, preferably 5 cm^2 to 100 cm^2, and more preferably 20 cm^2 to 60 cm^2. That area will vary, of course, with the amount of drug to be delivered and the flux of the drug through the body surface. Larger patches will be necessary to accommodate larger quantities of active agent, while smaller patches can be used for smaller quantities of active agent and/or active agents that exhibit a relatively high permeation rate.

[0108] Such drug delivery systems may be fabricated using conventional coating and laminating techniques known in the art. For example, adhesive matrix systems can be prepared by casting a fluid admixture of adhesive, active agent, and vehicle onto the backing layer, followed by lamination of the release liner. Similarly, the adhesive mixture may be cast onto the release liner, followed by lamination of the backing layer. Alternatively, the drug reservoir may be prepared in

the absence of drug or excipient, and then loaded by "soaking" in a drug/vehicle mixture. In general, these patches are fabricated by solvent evaporation, film casting, melt extrusion, thin film lamination, die cutting, or the like. The active agent will generally be incorporated into the device during patch manufacture rather than subsequent to preparation of the device.

[0109] In a preferred delivery system, an adhesive overlayer that also serves as a backing for the delivery system is used to better secure the patch to the body surface. This overlayer is sized such that it extends beyond the drug reservoir so that adhesive on the overlayer comes into contact with the body surface. The overlayer is useful because the adhesive/drug reservoir layer may lose its adhesion a few hours after application due to hydration. By incorporating such an adhesive overlayer, the delivery system remains in place for the required period of time.

[0110] Other types and configurations of topically applied drug delivery systems may also be used in conjunction with the present invention, as will be appreciated by those skilled in the art of transdermal drug delivery. See, for example, Ghosh, *Transdermal and Topical Drug Delivery Systems* (Interpharm Press, 1997), particularly Chapters 2 and 8.

V. ADMINISTRATION:

[0111] The method of delivery of the active agent may vary, but necessarily involves application of a formulation of the invention to an area of body surface affected with an inflammatory dermatosis. A cream, ointment, or lotion may be spread on the affected surface and gently rubbed in. A solution may be applied in the same way, but more typically will be applied with a dropper, swab, or the like, and carefully applied to the affected areas.

[0112] The dose regimen will depend on a number of factors that may readily be determined, such as severity of the dermatosis and responsiveness of the condition to be treated, but will normally be one or more doses per day, with a course of treatment lasting from several days to several months, or until a cure is effected or a diminution of disease state is achieved. One of ordinary skill may readily determine optimum dosages, dosing methodologies, and repetition rates. In general, it is contemplated that the formulation will be applied one to four times daily. With a skin patch, the device is generally maintained in place on the body surface throughout a drug delivery period, typically in the range of 8 to 72 hours, and replaced as necessary.

[0113] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. Other aspects, advantages, and modifications will be apparent to those skilled in the art to which the invention pertains. Furthermore, the practice of the present invention will employ, unless otherwise indicated, conventional techniques of drug formulation, particularly topical and transdermal drug formulation, which are within the skill of the art. Such techniques are fully explained in the literature. See *Remington: The Science and Practice of*

Pharmacy, cited *supra*, as well as Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed. (New York: McGraw-Hill, 1996).

EXPERIMENTAL

[0114] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of pharmaceutical formulation and the like, which are within the skill of the art. Such techniques are fully explained in the literature. In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.) but some experimental error and deviation should be accounted for. Unless otherwise indicated, temperature is in degrees Celsius and pressure is at or near atmospheric pressure at sea level. All reagents were obtained commercially unless otherwise indicated.

EXAMPLE 1

[0115] A topical gel of the invention is prepared by conventional pharmaceutical methods. The indicated amounts of the following ingredients are used:

Ingredient	Amount	
Purified water	600	grams
Polyethylene glycol	400	grams
Potassium hydroxide	0.01	gram
Edetate disodium	0.1	gram
Carbomer 934P	12.5	grams
Poloxamer 407	2.0	grams
Polysorbate 40	2.0	grams
Butylated hydroxytoluene	0.5	grams
Benzyl alcohol	10.0	grams

[0116] The carbomer 934P and the edetate disodium are added to 250 mL of the purified water, and the mixture is homogenized at low speed until the carbomer is dispersed. Next, the poloxamer 407, mixed with 250 mL of the purified water, is added to the carbomer mixture, and the resulting mixture is homogenized at low speed. The potassium hydroxide, dissolved in 100 mL of purified water, is added to this mixture, and the resulting mixture (Mixture 1) is homogenized at low speed. In a separate container, the polysorbate 40 and the butylated hydroxytoluene are added to the polyethylene glycol, and the resulting mixture is heated to 65°C and maintained at this temperature until all the compounds are dissolved; this mixture is then allowed to cool to room temperature, at which time the benzyl alcohol is added, and the resulting mixture is homogenized at low speed.

This mixture is then added to Mixture 1, and the resulting mixture is mixed at low speed until it is homogeneous, forming a gel of the invention.

EXAMPLE 2

[0117] A topical cream of the invention is prepared by conventional pharmaceutical methods. The indicated amounts of the following ingredients are used:

Ingredient	Amount	
Purified water	370	grams
White petrolatum	250	grams
Stearyl alcohol	250	grams
Propylene glycol	120	grams
Sodium lauryl sulfate	10	grams
Methylparaben	0.25	gram
Propylparaben	0.15	gram
Potassium hydroxide	0.01	gram

[0118] The stearyl alcohol and the white petrolatum are melted together on a steam bath, and then maintained at a temperature of approximately 75°C. The other ingredients are then added, after previously having been dissolved in the purified water and warmed to 75°C, and the resulting mixture is stirred until it congeals into a cream of the invention.

EXAMPLE 3

[0119] The formulations of Examples 1 and 2 in gel or cream form may be provided to patients having comedogenic and/or papulopustular lesions of acne. Each participating patient is instructed to topically apply a formulation of the invention on the involved areas of the skin such as forehead, face and chest. Three times daily administration is continued for 6 to 12 weeks.

[0120] The degree and rate of improvement on acne lesions is clinically evaluated. It is found that acne lesions consisting mainly of comedones improve substantially after 6

[0121] to 8 weeks of topical administration with the formulations of the invention. The time for complete clearing of comedogenic acne treated with the formulations of the instant invention will vary from 6 to 12 weeks.

EXAMPLE 4

[0122] The formulations of Examples 1 and 2 in a gel or cream form may be provided to patients having psoriasis afflicting multiple areas of the skin as well as the nails and scalp is selected for therapy. The patient weighs 80 kilograms and, other than the psoriasis, enjoys good health. Each

participating patient is instructed to topically apply the composition on the involved areas of the skin, nails and scalp twice a day.

[0123] The patient is monitored for improvement in the manifestations of psoriasis. The dosage is tapered and discontinued when the manifestations of psoriasis subside.

CLAIMS

1. A method of treating an individual afflicted with an inflammatory dermatosis, comprising topically applying to an affected area of the individual's skin a formulation comprised of a pharmaceutically acceptable topical carrier and a single active agent, wherein the single active agent is a pharmacologically active base and is present at a concentration sufficient to provide a formulation pH in the range of approximately 7.5 to 13.0.

2. The method of claim 1, wherein the inflammatory dermatosis is selected from the group consisting of allergic dermatoses, pruritic dermatoses, vascular dermatoses, sebaceous gland disorders, papulosquamous dermatoses, bacterial dermatoses, viral dermatoses, mycolic skin infections, granulomatous dermatoses, parasitic skin dermatoses, exfoliative dermatitis, bullous dermatoses, pigmented dermatoses, photosensitive dermatoses, dermatoses caused by collagen diseases, and dermatoses due to internal diseases.

3. The method of claim 2, wherein the inflammatory dermatosis is a sebaceous gland disorder.

4. The method of claim 3, wherein the sebaceous gland disorder is an acneiform disorder.

5. The method of claim 4, wherein the acneiform disorder is selected from the group consisting of acne vulgaris, acne conglombata, hidradenitis suppurativa, acne rosacea, seborrhea, seborrheic dermatitis, gram negative folliculitis, pyoderma faciale, steatocystoma multiplex, sebaceous hyperplasia, and rhinophyma.

6. The method of claim 5, wherein the acneiform disorder is acne vulgaris.

7. The method of claim 2, wherein the inflammatory dermatosis is a papulosquamous dermatosis.

8. The method of claim 7, wherein the papulosquamous dermatosis is psoriasis.

9. The method of claim 1, wherein the inflammatory dermatosis is an autoimmune condition.

10. The method of claim 9, wherein the autoimmune condition is atopic dermatitis, mast cell disease, bullous pemphigoid, pemphigus vulgaris, necrotizing vasculitis, discoid lupus erythematosus, systemic lupus erythematosis, or dermatitis herpetiformis.

11. The method of claim 1, wherein the pH is in the range of approximately 8.0 to 11.5.

12. The method of claim 22, wherein the pH is in the range of approximately 8.5 to 10.5.

13. The method of claim 1, wherein the formulation is aqueous.

14. The method of claim 13, wherein the aqueous formulation is selected from the group consisting of a cream, a gel, a lotion, and a solution.

15. The method of claim 14, wherein the aqueous formulation is a cream.

16. The method of claim 14, wherein the aqueous formulation is a gel.

17. The method of claim 14, wherein the aqueous formulation is a lotion.

18. The method of claim 14, wherein the aqueous formulation is a solution.

19. The method of claim 1, wherein the pharmacologically active base is a hydroxide-releasing agent.

20. The method of claim 19, wherein the pharmacologically active base is selected from the group consisting of inorganic hydroxides, inorganic oxides, metal salts of weak acids, and mixtures thereof.

21. The method of claim 20, wherein the pharmacologically active base is an inorganic hydroxide.

22. The method of claim 21, wherein the inorganic hydroxide is selected from the group consisting of ammonium hydroxide, alkali metal hydroxides, alkaline earth metal hydroxides, and mixtures thereof.

23. The method of claim 22, wherein the inorganic hydroxide is selected from the group consisting of ammonium hydroxide, sodium hydroxide, calcium hydroxide, potassium hydroxide, magnesium hydroxide, and mixtures thereof.

24. The method of claim 23, wherein the inorganic hydroxide is sodium hydroxide.

25. The method of claim 19, wherein the base is an inorganic oxide.

26. The method of claim 19, wherein the base is a metal salt of a weak acid.

27. The method of claim 1, wherein the pharmacologically active base is a nitrogenous base.

28. The method of claim 1, wherein the pharmacologically active base is an organic base.

29. The method of claim 28, wherein the organic base is selected from primary amines, secondary amines, tertiary amines, amides, oximes, nitrogen-containing heterocycles, and urea.

30. The method of claim 29, wherein the organic base is a primary amine, a secondary amine, or a tertiary amine.

31. The method of claim 30, wherein the organic base has the structure $NR^1R^2R^3$ wherein R^1, R^2 and R^3 are selected from H, alkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, hydroxyalkenyl, alkoxyalkenyl, cycloalkyl, cycloalkyl-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl, with the proviso that at least one of R^1, R^2, and R^3 is other than H.

32. The method of claim 30, wherein the organic base is selected from the group consisting of diethanolamine, triethanolamine, isopropanolamine, triisopropanolamine, dibutanol amine, tributanol amine, N-dodecylethanolamine, N-(2-methoxyethyl) dodecylamine, N-(2,2-dimethoxyethyl)dodecylamine, N-ethyl-N-(dodecyl)ethanolamine, N-ethyl-N-(2-methoxyethyl)dodecylamine, N-ethyl-N-(2,2-dimethoxyethyl) dodecylamine, dimethyldodecylamine-N-oxide, monolauroyl lysine, dipalmitoyl lysine, dodecylamine, stearylamine, phenylethylamine, triethylamine, PEG-2 oleamine, PEG-5 oleamine, dodecyl 2-(N,N-dimethylamino)propionate, bis(2-hydroxyethyl)oleylamine, and combinations thereof.

33. The method of claim 29, wherein the organic base is an amide.

34. The method of claim 33, wherein the amide has the structure R^4-(CO)-NR^5R^6 where R^4, R^5 and R^6 are independently selected from H, alkyl, cycloalkyl, cycloalkyl-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl.

35. The method of claim 34, wherein the amide is selected from the group consisting of hexamethyleneacetamide, hexamethyleneoctamide, hexamethylene lauramide, hexamethylene palmitamide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N,N-dimethyloctamide, N,N-dimethyldecamide, toluamide, dimethyl-m-toluamide, diethyl-m-toluamide, and combinations thereof.

36. The method of claim 29, wherein the organic base is a nitrogen-containing heterocycle.

37. The method of claim 36, wherein the nitrogen-containing heterocycle is selected from the group consisting of 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 1-propyl-3-dodecylpyrrolidine, 1-dodecyclazacycloheptan-2-one, ethylene thiourea, hydantoin, oxalylurea, imidazolidilyl urea, N-octadecyl morpholine, dodecylpyridinium, N-dodecylpyrrolidine, N-dodecylpiperidine, N-dodecylhomopiperidine, and combinations thereof.

38. The method of claim 1, wherein the formulation is applied periodically over an extended time period.

39. The method of claim 1, wherein the formulation is applied approximately twice weekly.

40. The method of claim 1, wherein the formulation is applied once daily.

41. The method of claim 1, wherein the formulation is applied twice daily.

42. The method of claim 1, wherein the formulation is applied on an as-needed basis.

43. The method of claim 38, wherein said extended time period is at least three months.

44. The method of claim 43, wherein said extended time period is at least four months.

45. A topical formulation for treating an inflammatory dermatosis, comprising a pharmaceutically acceptable topical carrier and a single active agent, wherein the single active agent is agent is a pharmacologically active base and is present at a concentration sufficient to provide a formulation pH in the range of approximately 7.5 to 13.0.

46. The formulation of claim 45, wherein the pH is in the range of approximately 8.0 to 11.5.

47. The formulation of claim 46, wherein the pH is in the range of approximately 8.5 to 10.5.

48. The formulation of claim 44, wherein the carrier is aqueous.

49. The formulation of claim 48, selected from the group consisting of a cream, a gel, a lotion, and a paste.

50. The formulation of claim 49, in the form of a cream.

51. The formulation of claim 49, in the form of a gel.

52. The formulation of claim 49, in the form of a lotion.

53. The formulation of claim 49, in the form of a paste.

54. The formulation of claim 45, wherein the pharmacologically active base is a hydroxide-releasing agent.

55. The formulation of claim 54, wherein the pharmacologically active base is selected from the group consisting of inorganic hydroxides, inorganic oxides, metal salts of weak acids, and mixtures thereof.

56. The formulation of claim 55, wherein the pharmacologically active base is an inorganic hydroxide.

57. The formulation of claim 56, wherein the inorganic hydroxide is selected from the group consisting of ammonium hydroxide, alkali metal hydroxides, alkaline earth metal hydroxides, and mixtures thereof.

58. The formulation of claim 57, wherein the inorganic hydroxide is selected from the group consisting of ammonium hydroxide, sodium hydroxide, calcium hydroxide, potassium hydroxide, magnesium hydroxide, and mixtures thereof.

59. The formulation of claim 58, wherein the inorganic hydroxide is sodium hydroxide.

60. The formulation of claim 55, wherein the base is an inorganic oxide.

61. The formulation of claim 55, wherein the base is a metal salt of a weak acid.

62. The formulation of claim 45, wherein the pharmacologically active base is a nitrogenous base.

63. The formulation of claim 45, wherein the pharmacologically active base is an organic base.

64. The formulation of claim 63, wherein the organic base is selected from primary amines, secondary amines, tertiary amines, amides, oximes, nitrogen-containing heterocycles, and urea.

65. The formulation of claim 64, wherein the organic base is a primary amine, a secondary amine, or a tertiary amine.

66. The formulation of claim 65, wherein the organic base has the structure $NR^1R^2R^3$ wherein R^1, R^2 and R^3 are selected from H, alkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, hydroxyalkenyl, alkoxyalkenyl, cycloalkyl, cycloalkyl-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl, with the proviso that at least one of R^1, R^2, and R^3 is other than H.

67. The formulation of claim 65, wherein the organic base is selected from the group consisting of diethanolamine, triethanolamine, isopropanolamine, triisopropanolamine, dibutanol amine, tributanol amine, N-dodecylethanolamine, N-(2-methoxyethyl) dodecylamine, N-(2,2-dimethoxyethyl)dodecylamine, N-ethyl-N-(dodecyl)ethanolamine, N-ethyl-N-(2-methoxyethyl)dodecylamine, N-ethyl-N-(2,2-dimethoxyethyl) dodecylamine,

dimethyldodecylamine-N-oxide, monolauroyl lysine, dipalmitoyl lysine, dodecylamine, stearylamine, phenylethylamine, triethylamine, PEG-2 oleamine, PEG-5 oleamine, dodecyl 2-(N,N-dimethylamino)propionate, bis(2-hydroxyethyl)oleylamine, and combinations thereof.

68. The formulation of claim 64, wherein the organic base is an amide.

69. The formulation of claim 68, wherein the amide has the structure R^4-(CO)-NR^5R^6 where R^4, R^5 and R^6 are independently selected from H, alkyl, cycloalkyl, cycloalkyl-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl.

70. The formulation of claim 69, wherein the amide is selected from the group consisting of hexamethyleneacetamide, hexamethyleneoctamide, hexamethylene lauramide, hexamethylene palmitamide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N,N-dimethyloctamide, N,N-dimethyldecamide, toluamide, dimethyl-m-toluamide, diethyl-m-toluamide, and combinations thereof.

71. The formulation of claim 64, wherein the organic base is a nitrogen-containing heterocycle.

72. The formulation of claim 71, wherein the nitrogen-containing heterocycle is selected from the group consisting of 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 1-propyl-3-dodecylpyrrolidine, 1-dodecyclazacycloheptan-2-one, ethylene thiourea, hydantoin, oxalylurea, imidazolidilyl urea, N-octadecyl morpholine, dodecylpyridinium, N-dodecylpyrrolidine, N-dodecylpiperidine, N-dodecylhomopiperidine, and combinations thereof.